MASSACHUSETTS

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Medical Policy

Immune Cell Function Assay

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Policy Number: 182

BCBSA Reference Number: 2.04.56 (For Plan internal use only)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Use of immune cell function assay testing to monitor and predict immune function after solid organ transplantation is considered **INVESTIGATIONAL**.

Use of immune cell function assay testing to monitor and predict immune function after hematopoietic stem cell transplantation is considered **INVESTIGATIONAL**.

Use of immune cell function assay testing for all other indications is considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO Blue[SM]	This is **not** a covered service.
Medicare PPO Blue[SM]	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81560	Transplantation medicine, measurement of donor and third party-induced CD154+T-cytotoxic memory cells
86352	Cellular function assay involving stimulation (e.g., mitogen or antigen) and detection of biomarker (e.g., ATP)

Description

Immunosuppression for Transplant

In current clinical practice, levels of immunosuppression in patients being managed after a solid organ transplant or hematopoietic cell transplantation are determined by testing for clinical toxicity (eg, leukopenia, renal failure) and by therapeutic drug monitoring when available. However, drug levels are not a surrogate for overall drug distribution or efficacy because pharmacokinetics often differ among individuals due to clinical factors such as underlying diagnosis, age, sex, and race; circulating drug levels may not reflect the drug concentration in relevant tissues; and serum level of an individual immunosuppressant drug may not reflect the cumulative effect of other concomitant immunosuppressants. The main value of therapeutic drug monitoring is the avoidance of toxicity. Individual immune profiles, such as an immune cell function assay, could support clinical decision making and help to manage the risk of infection from excessive immunosuppression and the risk of rejection from inadequate immunosuppression.

Treatment

Several commercially available tests of immune cell function have been developed to support clinical decision making.

ImmuKnow measures the concentration of adenosine triphosphate (ATP) in whole blood after a 15- to 18-hour incubation with phytohemagglutinin (a mitogenic stimulant). Cells that respond to stimulation show increased ATP synthesis during incubation. Concurrently, whole blood is incubated in the absence of stimulants for the purpose of assessing basal ATP activity. CD4-positive T lymphocytes are immunoselected from both samples using anti-CD4 monoclonal antibody-coated magnetic particles. After washing the selected CD4-positive cells on a magnet tray, a lysis reagent is added to release intracellular ATP. A luminescence reagent added to the released ATP produces light measured by a luminometer, which is proportional to the concentration of ATP. The characterization of the cellular immune response of a specimen is made by comparing the ATP concentration for that specimen with fixed ATP production ranges.

Pleximmune measures CD154 expression on T-cytotoxic memory cells in patient's peripheral blood lymphocytes. CD154 is a marker of inflammatory response. To characterize the risk of rejection, the patient's inflammatory response to transplant donor cells is expressed as a fraction of the patient's inflammatory response to third-party cells. This fraction or ratio is called the Immunoreactivity Index (IR).

If the donor-induced response exceeds the response to third-party cells, the individual is at increased risk for rejection. Cells are cultured and then analyzed with fluorochrome-stained antibodies to identify the cells expressing CD154. For posttransplant blood samples, an IR greater than 1.1 indicates an increased risk of rejection, and an IR less than 1.1 indicates a decreased risk of rejection. For pretransplant samples, the threshold for IR is 1.23.

Summary

Careful monitoring of lifelong immunosuppression is required to ensure the long-term viability of solid organ allografts without incurring an increased risk of infection. The monitoring of immunosuppression parameters attempts to balance the dual risks of rejection and infection. It is proposed that individual immune profiles, such as an immune cell function assay, will help assess the immune function of the transplant recipient and individualize immunosuppressive therapy.

Summary of Evidence

For individuals with a solid organ transplant or hematopoietic cell transplant who receive immune cell function assay testing with ImmuKnow, the evidence includes numerous studies on the association between assay test values and subsequent rejection or infection, and a randomized controlled trial in liver transplant patients. Relevant outcomes are overall survival, other test performance measures, and morbid events. The ImmuKnow test has shown variable associations with infection and rejection, depending on the type of transplant and context of the study. Across all the studies among various types of patients, ImmuKnow levels are associated with the risk of rejection when levels are high and risk of infection when levels are low. However, the absolute risk and increments of risk are uncertain because of the heterogeneity of the studies. The predictive characteristics of the test are still uncertain and do not allow a strong chain of evidence for clinical utility. The trial of the ImmuKnow test in liver transplant patients showed improvement in overall survival; however, the trial had several limitations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a solid organ transplant or hematopoietic cell transplant who receive immune cell function assay testing with Pleximmune, the evidence includes the U.S. Food and Drug Administration (FDA) documentation and a report on the test's development and validation. Relevant outcomes are overall survival, other measures of test performance, and morbid events. Small studies have shown that Pleximmune values correlate with long-term survival. Pleximmune test results correlated with rejection, but conclusions are uncertain because of extremely limited evidence deriving from a small number of patients described briefly in the FDA approval documents and a second study, in which the confidence interval bounds for sensitivity and specificity estimates were wide. No direct studies of clinical utility were identified. An argument for clinical utility using a chain of evidence would rely on both a demonstration of clinical validity and a rationale that specific clinical interventions based on the results of the test decrease the risk of a poor health outcome. At present, the clinical interventions that would occur as a result of the test result are uncertain, and so the clinical validity is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
2/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2022	Clarified coding information.
2/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
2/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2018	Annual policy review. New references added.
1/2017	Annual policy review. New references added.
2/2016	Annual policy review. New references added.

11/2015	Added coding language.
12/2014	Annual policy review. New references added.
2/2014	Annual policy review. New references added.
11/2011-4/1012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/2011	References added.
11/2010	Medical Policy Group- Gastroenterology, Nutrition and Organ Transplantation No changes to policy statements.
5/2010	New medical policy. Effective 5/1/2010.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

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